PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

23/7

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000502	19.01.2005	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D403/04, C07D401/14

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000502

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4, 15, 16 (w.r.t. novelty, inventive step, industrial applicability), 14, 17 (w.r.t. industrial applicability)

because:

☒ the said international application, or the said claims Nos. 14, 17 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-4, 15, 16

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000502

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-14, 17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-14, 17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	5-13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1-4 relate to compounds defined by reference to a certain selectivity.
The use of such a parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameter the Applicants have chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.
In addition, present claims 1-4 relate to compounds defined by reference to a desirable characteristic or property, namely the above-mentioned selectivity.
The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved.
Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, an exhaustive and complete search is precluded for practical and economical reasons. The search was based upon though not limited to the remaining claims, examples and tables given in the description (cf. Arts. 6, 15 and Rule 33 PCT).

Claims 14 and 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims 15 and 16 could not be searched, since they are missing in the file and since the Applicants failed to either submit the said missing claims or to at least correct the numbering of the present claims in due time.

Re Item IV

Lack of unity of invention

The document D1 (see paragraph "novelty" below) discloses indolylmaleimide derivatives

as CDK inhibitors. These compounds have in common the same structural feature as the compounds of Formula I of the present claim 5, namely indolylmaleimide having an aromatic substituent "R".

Hence, the distinguishing feature between the said compounds of Formula I and the said compounds of D1 has to be seen as the particular kind of substituent R, namely

- firstly naphthyl and
- secondly 3- or 4-pyridyl.

However, with the presence of two different distinguishing features and with the umbrella of any common structural feature being lost, the subject-matter of the searched claims can no longer be regarded as being unitarian within the meaning of Rule 13.1. PCT and is therefore split into two different inventions (non-unity a posteriori), the said inventions being as follows:

- provision of a compound of Formula I having naphthyl substitution, method for its preparation and its medical use (first invention) and
- provision of a compound of Formula I having 3- or 4-pyridyl substitution, method for its preparation and its medical use (second invention).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 02/38561 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; ALBER) 16 May 2002 (2002-05-16)

Novelty

The document D1 discloses indolylmaleimide derivatives as CDK inhibitors which structurally differ from the compounds of claim 5 in that they lack any pyridine substituent and in that the naphthyl substituent is permanently substituted at position 3 (see page 1, title; page 1, Formula I; page 40, paragraph 2; page 41, last paragraph - page 42, first paragraph; Examples 28-52).

In view of this prior art, novelty has to be acknowledged for the subject-matter of the independent claims 5, 8-14 and 17 and the dependent claims 6 and 7.

Inventive step

The distinguishing feature between the novel subject-matter of the ***first invention*** and D1 is the fact that the naphthyl group is permanently substituted at position 7.

The distinguishing feature between the novel subject-matter of the ***second invention*** and D1 is the presence of 3- or 4-pyridyl as substituent "R".

In the absence of any evidence for an unexpected technical effect linked to both features, the objective problem underlying the novel subject-matter of both inventions can merely be seen as the provision of further compounds suitable as CDK inhibitors.

For the ***first invention***, the claimed solution to this very general problem was the modification of the naphthyl derivatives already known from D1 by "shifting" the permanent substituent from position 3 towards position 7.

For the ***second invention***, the claimed solution was the replacement of the pyrimidine group already known from D1 with pyridine.

However, since both solutions were not derivable from D1, the presence of inventive step has to be acknowledged for the novel subject-matter of both inventions, even in the absence of a technical effect.

Industrial applicability

There is no doubt that the subject-matter of the present claims 4-13 is industrially applicable.

However, for the assessment of the present claims 14 and 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2005/000502

Certain defects in the international application

Apparently, clerical error appears on page 13 of the description: it should have read WO03/82858 instead of WO03/08259.

Re Item VIII

Certain observations on the international application

The breadth of a claim should be such that it could be expected that all possibilities comprised would actually solve the problem underlying the application. Consequently, a claim should only include such possibilities (and their reasonable generalisations) which have been made credible in the specification. It appears thus that open definitions such as "aryl" and "heterocyclic residue" (see claim 5) go far beyond what has actually been verified in the worked Examples on file.

Moreover, a person skilled in the art cannot assume that all those possibilities which are presently comprised would be suitable in the sense of solving the present problem.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

28/7

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000502	19.01.2005	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D403/04, C07D401/14

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000502

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000502

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4, 15, 16 (w.r.t. novelty, inventive step, industrial applicability), 14, 17 (w.r.t. industrial applicability)

because:

☒ the said international application, or the said claims Nos. 14, 17 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-4, 15, 16

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000502

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-14, 17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-14, 17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	5-13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1-4 relate to compounds defined by reference to a certain selectivity.
The use of such a parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameter the Applicants have chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.
In addition, present claims 1-4 relate to compounds defined by reference to a desirable characteristic or property, namely the above-mentioned selectivity.
The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved.
Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, an exhaustive and complete search is precluded for practical and economical reasons. The search was based upon though not limited to the remaining claims, examples and tables given in the description (cf. Arts. 6, 15 and Rule 33 PCT).

Claims 14 and 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims 15 and 16 could not be searched, since they are missing in the file and since the Applicants failed to either submit the said missing claims or to at least correct the numbering of the present claims in due time.

Re Item IV

Lack of unity of invention

The document D1 (see paragraph "novelty" below) discloses indolylmaleimide derivatives

as CDK inhibitors. These compounds have in common the same structural feature as the compounds of Formula I of the present claim 5, namely indolylmaleimide having an aromatic substituent "R".

Hence, the distinguishing feature between the said compounds of Formula I and the said compounds of D1 has to be seen as the particular kind of substituent R, namely

- firstly naphthyl and
- secondly 3- or 4-pyridyl.

However, with the presence of two different distinguishing features and with the umbrella of any common structural feature being lost, the subject-matter of the searched claims can no longer be regarded as being unitarian within the meaning of Rule 13.1. PCT and is therefore split into two different inventions (non-unity a posteriori), the said inventions being as follows:

- provision of a compound of Formula I having naphthyl substitution, method for its preparation and its medical use (first invention) and
- provision of a compound of Formula I having 3- or 4-pyridyl substitution, method for its preparation and its medical use (second invention).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 02/38561 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; ALBER) 16 May 2002 (2002-05-16)

Novelty

The document D1 discloses indolylmaleimide derivatives as CDK inhibitors which structurally differ from the compounds of claim 5 in that they lack any pyridine substituent and in that the naphthyl substituent is permanently substituted at position 3 (see page 1, title; page 1, Formula I; page 40, paragraph 2; page 41, last paragraph - page 42, first paragraph; Examples 28-52).

In view of this prior art, novelty has to be acknowledged for the subject-matter of the independent claims 5, 8-14 and 17 and the dependent claims 6 and 7.

Inventive step

The distinguishing feature between the novel subject-matter of the ***first invention*** and D1 is the fact that the naphthyl group is permanently substituted at position 7.

The distinguishing feature between the novel subject-matter of the ***second invention*** and D1 is the presence of 3- or 4-pyridyl as substituent "R".

In the absence of any evidence for an unexpected technical effect linked to both features, the objective problem underlying the novel subject-matter of both inventions can merely be seen as the provision of further compounds suitable as CDK inhibitors.

For the ***first invention***, the claimed solution to this very general problem was the modification of the naphthyl derivatives already known from D1 by "shifting" the permanent substituent from position 3 towards position 7.

For the ***second invention***, the claimed solution was the replacement of the pyrimidine group already known from D1 with pyridine.

However, since both solutions were not derivable from D1, the presence of inventive step has to be acknowledged for the novel subject-matter of both inventions, even in the absence of a technical effect.

Industrial applicability

There is no doubt that the subject-matter of the present claims 4-13 is industrially applicable.

However, for the assessment of the present claims 14 and 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2005/000502

Certain defects in the international application

Apparently, clerical error appears on page 13 of the description: it should have read WO03/82858 instead of WO03/08259.

Re Item VIII

Certain observations on the international application

The breadth of a claim should be such that it could be expected that all possibilities comprised would actually solve the problem underlying the application. Consequently, a claim should only include such possibilities (and their reasonable generalisations) which have been made credible in the specification. It appears thus that open definitions such as "aryl" and "heterocyclic residue" (see claim 5) go far beyond what has actually been verified in the worked Examples on file.

Moreover, a person skilled in the art cannot assume that all those possibilities which are presently comprised would be suitable in the sense of solving the present problem.